Remarks

Entry of the amendment is respectfully requested since it would lessen the issues on appeal or avoid the need for appeal.

Claims Amendment

Claims 16, 18-20 and 36 are pending. Claim 16 is amended to recite the bioavailability improvement over the standard Lipanthyl®200M. This amendment is supported by figure 1 and its description, and example 3 (including table 1) and the conclusion stated at page 12, line 16. No new matter is added. Recitation of trademark is permitted, see MPEP at 608.01(v). Indeed, the Lipanthyl®200M has a meaning which is well known and satisfactorily defined in the literature, and this at the time of priority (Lipanthyl®200M was indeed on sale many years before the priority date of the instant application.).

Claim 41 is added, which is directed to the assessment of bioavailability. Table 1 lists C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$ as possible parameters, the last two being collectively referred to as "AUC" (AUC_{0-t}, $AUC_{0-\infty}$, sometimes also referred simply as AUC_t and AUC_∞ are the Area Under the plasma Curve from administration to last observed concentration at time t and extrapolated to infinite time, respectively). Claim 41 is directed to two parameters, AUC and C_{max}, useful for the assessment of bioavailability. Two main criteria are used when determining bioavailability (and subsequently bioequivalence), which are AUC and C_{max}, Area Under Curve and peak concentration, respectively. These two criteria are the main technical features, as can be seen from the extract of the two attached documents from the US FDA. These two documents, albeit having a date which is after the priority date of the instant application represent what the skilled addressee would have understood at the time of filing. In both documents, AUC and Cmax are the two main characteristics. See especially the document entitled "*Guidance for Industry, Bioequivalence Guidance*", page 2 which discloses "*AUC and CMAX as the pivotal parameters for bioequivalence determination*" (Attachment A). See also especially the document "*Statistical Approaches to Establishing Bioequivalence*", at page 2 (Attachment B). The skilled man would also consider the corresponding EU regulations, as evidence by the attached document issue by EMEA, entitled "*Note for Guidance on the Investigation of*

bioavailability and Bioequivalence", especially at section 3.6.2 (Attachment C). No new matter is added.

Claim 42 is added, which is the combination of amended claim 16 and new claim 41. New claims 43 to 45 (now dependant upon new claim 42) correspond to old claims 18-20. New claim 46 is directed to the specific tablet of claim 42, which is once-daily and where the bioavailability is assessed by both AUC and C_{max}. New claims 47 and 48 correspond to old claims 19 and 20. No new matter is added.

The Interview

The Examiner is thanked for the advice and courtesies extended during the personal interview held on 26 June 2008. A copy of the Interview Summary form, PTOL-413, was provided to Applicants' representative at the close of the interview. The content set forth on the PTOL-413 is accurate. In addition, a copy of proposed amendments to claim 1 was given to the Examiner as was a flow chart illustrating the relationship between the applications in this family. As requested, an IDS citing the "Guichard" article, ("A New Formulation of Fenofibrate: Suprabioavailable Tablets," Current Medical Research & Opinion, Vol. 16, No. 2, 2000, pp.134-138.), is enclosed with this response. The "Guichard" article is not prior art to this application due to its date of publication and the priority claimed herein.

The Invention

Before addressing each rejection in more details, a review of the invention and the conditions of its genesis should be made.

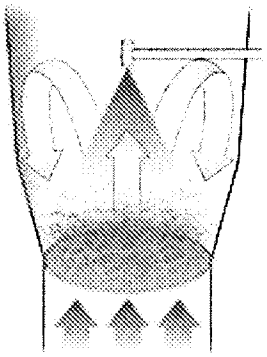
Fenofibrate is a known drug for treating hypercholesterolemia. It was first available as capsule of 300mg. Then a first improvement occurred through the drug Lipanthyl®200M. Lipanthyl®200M is considered the standard in the art of fenofibrate as all bioequivalence studies are generally presented with respect to this standard. Lipanthyl®200M is a capsule comprising fenofibrate which has been co-micronized together with a (solid) surfactant. This specific co-

micronization is the subject of Curtet, abundantly discussed in the specification through reference to the European counterpart (EP'532). This technique allows higher bioavailability which, in turns allows lowering the dose of active while retaining the same effectiveness. See the discussion in the introductory part of the specification on the EP'532 patent. Thus, there has been a trend to lower the amount of active drug while achieving the same therapeutical effects.

The invention allows a further lower dose, compared to the 200mg of Lipanthyl®200M, thanks to an improved bioavailability. This improved bioavailability of the composition is achieved thanks to a novel process which is the subject of the instant application. See the application as filed, at page 7, lines 21-24.

> "The method according to the invention consists in using the fluidized bed granulation principle, but with specific starting materials, in order to arrive at an improved dissolution profile and thus, at elevated bioavailability. In particular, the invention employs a suspension of the micronized active ingredient in a solution of a hydrophylic polymer and, optionally, a surfactant."

A review of the prior art granulation technique appears also necessary at this stage. Wet granulation is a technique widely used in the field of pharmaceuticals. Curtet uses this technique of wet granulation starting from co-micronized fenofibrate and adding about 8.9% water. Another technique that is used is a spraying technique, especially fluidized bed granulation. This technique is used for example in a bed granulator as exemplified below. The dry starting material (the powder side) is placed in the product container. The dry material comprises in the prior art the active ingredient and the support (typically lactose). Here it is mixed vigorously in the heated gas stream, held in suspension and agglomerated/granulated by spraying with a suitable solution of a binder (the liquid side). The product is then dried to the required moisture.
A schematic representation of a fluid bed granulator is found below (embodiment is top spray).



This technique is well known in the art. This is recalled in the specification at page 7, lines 25-31.

> "The fluidized-bed granulation technique is widely used in the pharmaceutical industry for preparing capsules or tablets. Conventionally, according to the prior art, a powder or a mixture of powders (active ingredient + excipients) is put into suspension in the fluidized bed in a granulator, and a solution containing a binder and, optionally, a surfactant, is sprayed onto this bed to form granules. The fluidized-bed granulation technique is well known to those skilled in the art and reference should be made to standard works such as for example "Die Tablette", by Ritschel, Ed. Cantor Aulendorf, pages 211-212. "

The invention is based on the discovery that part of the powder side (here the active ingredient) should be placed in the liquid side. This is indicated in the cited paragraph at page 7 lines 21-24 referred to above as well in the first paragraph at page 8:

> "The invention, as has been indicated, comprises spraying a suspension of an active ingredient micronized with a hydrophilic polymer onto an inert carrier. [...]"

The result is a specific granule, which appears to be an inert support coated with active ingredient. This is also indicated in the top paragraph at page 8:

> "[...] Following granulation, the granulate formed consists of crystals of, for example, lactose, which are isolated (or possibly agglomerated together by the spray solution) and particles of active ingredient and PVP adhering to the crystal surface. The granulate could similarly be constituted of coated crystals which are agglomerated, or even of such an agglomerate having received a coating."

This granule exhibits then a specific dissolution profile as well as increased bioavailability. Inventors view this as a surprising result. Fluidized bed granulation was known generally as a granulation technique and there having all powders (including the active ingredient) in the powder side generally provides granules having a bioavailability which is comparable to granules obtained using other granulation techniques such as wet granulation (as in Curtet). It has been found surprising that having part of the powder (here the active ingredient) in the fluid provides specific granules with enhance bioavailability. The term "suprabioavailable" can be used to define this improved bioavailability. Nothing in the prior art could suggest such an improvement.

This is summarized in a journal publication, the "Guichard" article regarding the evolution of the fenofibrate-containing drugs. Figure 1 of Guichard provides the dissolution profiles of the 300mg formulation, the Lipanthyl®200M formulation (with a hand-written reference to the EP'532) and the invention (with a hand written reference to the French priority number). This figure makes it clear that the instant invention provides a great improvement over the prior art, leading to suprabioavailability.

Guichard then continues on and states in the paragraph entitled "Increasing the bioavailability", with reference to figure 2:

> "This process yields fast and free access of the drug particle to the solubilisation medium by dispersing [...]. Dispersion is achieved by coating micronized fenofibrate particles directly onto an inert excipient core instead of allowing them to aggregate randomly to excipients. As a result, the micronized fenofibrate particles are immediately exposed to the dissolution medium and a significant increase of the dissolution rate from the tablet is achieved."

As a result, the bioavailability is increased as is stated in the paragraph "results of pharmacokinetic studies"

> "Pharmacokinetic studies in healthy volunteers have demonstrated that this technological improvement induced a further 25% increase in bioavailability. [..] the microcoating process not only improved the bioavailability but also provided a better pharmacokinetic profile. [...] The new suprabioavailable tablet incorporating both the micronisation technology and the micro-coating process yielded a further 24% reduction in plasma variability."

The Guichard article attributes the superiority of the suprabioavailable formulation to the microcoating process.

The invention is further directed to the manufacture of tablets. Tablets provide superior results compared to the capsules of the prior art (both the Lipanthyl®300mg and the Lipanthyl®200M are capsules).

Indeed, as stated in the Guichard article, in the last full paragraph section before the "conclusion" section, a tablet brings additional benefits over a capsule.

Thus, there is ample showing of the superiority of the suprabioavailable tablet and process for making the same.

The Rejections

All claims stand rejected over Krause in view of Deboeck or alternatively over Ghebre-Sellassie in view of Krause and further in view of Deboeck.

The rejection appears to flow from a literal reading of the claim prior to amendment. The amendment renders the rejections moot.

Krause is directed to compositions comprising fenofibrate and an ACAT inhibitor. Krause indicated that the compositions may comprise from 300 to 1200mg of fenofibrate. Given the date of Krause, this obviously corresponds to Lipanthyl®300, the first fenofibrate product generation; this also flows from the lack of indication of micronization for the active ingredient fenofibrate, which is thus presumed to be present under the non-micronized state (typical particle size would then be 50-200μm). Examples directed to immediate-release tablets, i.e. examples 5-10, all use at least 300mg of fenofibrate. The process for making the tablets is a standard wet-granulation technique, which is a standard technique distinct from the new process used of the invention. To conclude, the Krause tablets should be at best bioequivalent to the Lipanthyl®300, the first generation of fenofibrate drugs. As a point of distinction, the Krause tablets are not even bioequivalent to Lipanthyl®200M, let alone superior to them.

Ghebre-Sellassie is directed to gemfibrozil and not to fenofibrate. Ghebre-Sellassie is directed to a specific embodiment where the tablet will have both an immediate-release part and a sustained-release part in it, obtained thanks to two different granulations. The granulation technique used for the immediate-release part (the first granulation in Ghebre-Sellassie) is a conventional wet granulation technique. What has been said above with respect to Krause can also be stated for Ghebre-Sellassie, since there is no indication of particle size and since the date of Ghebre-Sellassie is contemporary to Krause. Ghebre-Sellassie also uses an amount of hydrophilic polymer (see at col.2, first paragraph and example 1) which is low. 6.4 parts of cellulosic polymer is used together with 255.5 parts of active, i.e. about 2.5%. This amount should be compared to that used in the invention, which is unusually high. The amount of drug that is used in Ghebre-Sellassie is not indicated in terms of amount per dosage unit. To conclude on Ghebre-Sellassie, the tablets disclosed are even farther remote from the invention when compared to Krause.

Krause and Ghebre-Sellassie at best disclose a formulation that would be, in terms of bioavailability, at best comparable to the first generation, Lipanthyl®300.

Deboeck is directed to fenofibrate composition, and more specifically to a generic of Lipanthyl®200M. Indeed, column 8 referred to by the Examiner discloses (see table) fed and fasted bioequivalency tests between the Deboeck composition and Lipanthyl®200M. Note that Lipenthyl®200M is to be administered under fed conditions (i.e. at the time of the meal of shortly thereafter) and the fed conditions appear more appropriate for a comparison. It flows from the date given, notably AUC and C_{max}, (181 v. 184. 7 and 11.1 v. 10.9, respectively) that the Deboeck composition is bioequivalent to Lipanthyl®200M. Thus, Deboeck discloses a composition which has the same bioavailability as Lipanthyl®200M. Further, Deboeck is directed to capsules and not to a tablet (the Deboeck formulations simply cannot be processed into tablets).

The invention is directed to a composition which has a bioavailability that is greater than that of Lipanthyl®200M. Krause and Ghebre-Sellassie provide tablets having a bioavailability that is lesser than that of Lipanthyl®200M. Deboeck provides capsules having the same bioavailability as Lipanthyl®200M. Thus, none of the documents, either individually or in

combination render the instant invention obvious. The invention is directed to (i) fenofibrate tablets which are (ii) suprabioavailable when compared to Lipanthul®200M.

Summary

An early and favorable consideration and allowance of the pending claims is respectfully requested.

Respectfully submitted,

By _____

Date: July 23, 2008

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PTO/SB/22 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2008 **(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)**	Docket Number (Optional) 31672-224622
Application Number 10/665,522 ~~ Conf. No.: 5813	Filed September 22, 2003
For FENOFIBRATE COMPOSITIONS HAVING ENHANCED BIOAVAILABILITY	
Art Unit 1618	Examiner Sheikh, Humera N.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application. The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☐	Two months (37 CFR 1.17(a)(2))	$460	$225	$
☒	Three months (37 CFR 1.17(a)(3))	$1050	$525	$ **1050.00**
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number **22-0261** . I have enclosed a duplicate copy of this sheet.

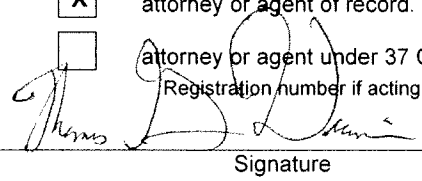
I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 35,046

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____ .



Signature — July 23, 2008 (Date)

Thomas G. Wiseman (Typed or printed name) — (202) 344-4614 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of 1 forms are submitted.

#972455

PTO/SB/31 (10-07)
Approved for use through 10/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES	Docket Number (Optional) 31672-224622

In re Application of	STAMM et al.
Application Number	10/665,522 ~~ Conf. No. 5813
Filed	September 22, 2003
For	FENOFIBRATE COMPOSITIONS HAVING ENHANCED BIOAVAILABILITY
Art Unit	1618
Examiner	Sheikh, Humera N.

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

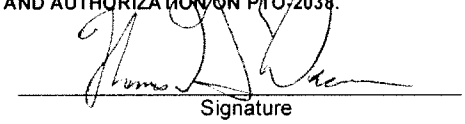
The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ **510.00**

- [ ] Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____
- [ ] A check in the amount of the fee is enclosed.
- [ ] Payment by credit card. Form PTO-2038 is attached.
- [ ] The Director has already been authorized to charge fees in this application to a Deposit Account. I have enclosed a duplicate copy of this sheet.
- [X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **22-0261** .
- [X] A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed (3 months eot).

WARNING: INFORMATION ON THIS FORM MAY BECOME PUBLIC. CREDIT CARD INFORMATION SHOULD NOT BE INCLUDED ON THIS FORM. PROVIDE CREDIT CARD INFORMATION AND AUTHORIZATION ON PTO-2038.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 35,046
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____



Signature

Thomas G. Wiseman
Typed or printed name

(202) 344-4614
Telephone number

July 23, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

- [X] *Total of 1 forms are submitted.

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